THE PENETRATION OF ANTIBIOTICS INTO PERITONEAL FLUID*

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SELECTION of an antibiotic for treatment of peritonitis or intra-abdominal abscess should reflect both the drug's spectrum of antibacterial activity and its ability to penetrate the peritoneum. Should the penetration of the peritoneum by the antibiotic be inadequate, administration directly into the peritoneum may be indicated. We have recently investigated the penetration of two groups of antibiotics into peritoneal fluid obtained experimentally through chambers implanted in rabbits.

METHODS

Our method for obtaining peritoneal fluid utilized the subcutaneously implanted tissue capsule studied extensively by Guyton[1] and others. For our purposes, ordinary table-tennis balls were drilled with approximately 200 holes 1/16 inch in diameter. Under intravenous anesthesia four or five chambers were placed in adult rabbits intraperitoneally through a midline abdominal incision.

In two to four weeks the chambers were firmly attached to the bowel or omentum of the rabbits and completely encased internally and on the outer surface by a thin layer of connective tissue. The tissue was supplied by blood vessels extending from the bowel or omentum through the capsular perforations at the point of attachment. The

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remaining space in the capsules had become filled with fluid which was easily aspirated through the abdominal wall with a 20 or 22 gauge needle. Bloody aspirates were considered traumatic and were discarded. The capsular fluid had the following characteristics (arithmetic mean value): leukocytes, 1,560/mm.^{3}; neutrophiles, 55%; 11,550 erythrocytes/mm.^{3}; *p*H 7.37; and protein 4.1 gm./100 ml. The value for protein is higher than the average for fluid aspirated from chambers placed subcutaneously in dogs.[2]

The antibiotics administered were either cephalosporins (protein-bound) or aminoglycosides (free or poorly bound).[3]

Cephalosporins were given intramuscularly in a dose of 30 mg./kg. and aminoglycosides were given intramuscularly or intravenously in a dose of two to three mg./kg. (gentamicin and tobramycin) or 7.5 mg./kg. (amikacin). Samples of blood serum and chamber fluid were obtained 30 minutes after injection of the antibiotic, then at six hourly intervals, and again at 24 hours. The levels of antibiotic were assayed *in vitro* by diffusion from paper discs on Mueller Hinton agar plates using *Staphylococcus* (strain 6538P) or spores of *Bacillus subtilis* as indicators. Standard curves were prepared with pooled rabbit serum. For each study mean values were calculated for six to 10 capsular fluids and three to five samples of serum.

Results

Cephalosporins. 1) Cefazolin is about 86% bound to serum protein.[4] At 30 minutes the very high peak serum level of 114 mcg./ml. was attained. The peritoneal level was much lower and reached its peak at about 13.6 mcg./ml. in four to five hours. The level was still 2.8 mcg./ml. in the capsular fluid after 24 hours. The results indicated both a slow uptake and slow exit from the chambers. The mean peak level attained in the chamber was 11.9% of the mean peak achieved in the serum. 2) Cephalothin is about 65% bound to serum protein.[4] The peak serum level after intramuscular injection was 21.7 mcg./ml. in 30 minutes. The peak level in the chamber fluid was 5.7 mcg./ml. and was reached in one to two hours. The mean peak achieved in the fluid was 26.6% of the mean peak in the serum. No detectable antibiotic remained in the chamber after 24 hours.

Aminoglycosides. 1) For gentamicin the peak serum level was 8.6 mcg./ml. and the peak capsular fluid level was 1.4 mcg./ml. The ratio

of capsular fluid peak to serum peak was only 16.5%. 2) Tobramycin produced serum and capsular peak levels which were almost the same as those seen with gentamicin. 3) Amikacin (BB-K8) was given in a substantially larger dose (7.5 mg./kg.). Therefore, the peak serum level was much higher (22.4 mcg./ml.). More important, the peak capsular fluid level was 7.3 mcg./ml., which was 32.4% of the peak serum level. The decay of amikacin in serum in these rabbits was slower ($t\frac{1}{2}$ [biological half life] = 2 hr.) than observed with gentamicin and tobramycin ($T\frac{1}{2}$ = 1½ hr.). Amikacin, like gentamicin and tobramycin, is active against *Pseudomonas* and resembles kanamycin in its structure and pharmacokinetics. Cohn[5] has also found kanamycin to have a good penetration into the peritoneal cavity.

Discussion

The penetration of antibiotic into extravascular tissues may be governed by several factors, including: 1) concentration gradient from serum to tissue fluid, 2) binding to proteins in serum and tissues, 3) diffusibility (molecular size and pK value), and 4) lipid solubility.

Our initial studies with the chamber model of peritoneal tissue in normal rabbits have shown that the aminoglycosides gentamicin and tobramycin (unbound to serum proteins) do not penetrate into capsular fluid as well as might be expected. Certainly there was not better uptake than with the more highly protein-bound cephalosporins when peak capsule levels were compared to peak serum levels. Cefazolin, the cephalosporin, which was the most highly protein-bound drug tested (86%), achieved the lowest ratio of capsular peak to serum peak, but still showed a substantial level of drug in capsular fluid (13.6 mcg./ml.). Factors such as a higher serum peak level and a longer half-life than cephalothin may offset the effect of high protein binding. Similarly, the longer half-life of amikacin when compared to tobramycin and gentamicin may be responsible for better penetration of this drug. The amount of antibiotic transported in the protein-bound state and the degree of binding of antibiotic to proteins within the capsules is not known.

Summary

Perforated table-tennis balls were implanted in the peritoneal cavities of rabbits. After two to four weeks fluid could be aspirated easily

from the chambers by percutaneous puncture. Comparisons were made of penetration of the chamber fluid using the protein-bound cephalosporin antibiotics (cephalothin and cefazolin) and poorly-bound aminoglycosides (gentamicin, tobramycin, and amikacin). The ratio of the peak chamber-fluid level to peak serum level was not substantially less in the case of the cephalosporins than observed with the aminoglycosides.

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